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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/234,028 | 01/20/1999 | RONALD T. RAINES | 960296.95360 | 6579 |

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| EXAMINER | |
|---|---|
| HUTSON, RICHARD G | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/234,028 | RAINES, RONALD T. | |
| | Examiner | Art Unit | |
| | Richard G. Hutson | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



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## DETAILED ACTION

Applicants amendment of the specification and claims 2 and 15, in the paper of 4/14/2005, is acknowledged. Claims 1-15 are at issue and are present for examination.

Applicants' arguments filed on 4/14/2005, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 11-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

It is noted that each of the following rejections under 112 first paragraph were previously made in the office action dated 1/2/2001. While it was determined that the amendments and response submitted on 7/5/2001, overcame the rejections based on a lack of written description, and a lack of enablement for the full scope of the claimed subject matter, upon further consideration these rejections have been re-instated.

The rejections are restated below as the apply to new claims 1-10 and 15.

Claims 1-10 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-10 and 15 are directed to all possible mutant ribonuclease inhibitors having at least one amino acid substitution in at least one of its adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease (claim 1) or angiogenin (claim 9), wherein said substituted cysteine residue is in at least one of positions 95, 96, 329 and 330 (claims 2, 10 and 15), wherein said cysteine residue is substituted with an alanine residue (claim 3), wherein said cysteine residue substitution inhibits formation of a disulfide bond (claim 4), wherein said mutant is 10 to 15 fold more resistant to oxidative damage than the native human ribonuclease inhibitor (claim 5), wherein the ribonuclease is of the RNase A superfamily (claim 6), wherein said RI inhibits ribonucleolytic activity in vitro (claim 7), wherein said mutant ribonuclease inhibitor is derived from the native human ribonuclease inhibitor (claim 8). The specification, however, only provides the representative species in which the cysteines at amino acid positions 95, 96, 329 and 330 of human ribonuclease inhibitor having the amino acid sequence of SEQ ID NO: 3, are mutated to alanines, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional

representative species of these mutant ribonuclease inhibitors by any identifying structural characteristics or properties other than the activities recited in claim 1 and the disclosed cysteine modifications, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants traverse this rejection in combination with the lack of scope of enablement rejection stated below. Applicants comments will be dealt with below following the lack of scope of enablement rejection.

As stated above, the following rejection under 112 first paragraph was previously made in the office action dated 1/2/2001and applicants amendments and response submitted on 7/5/2001 upon further consideration have been determined insufficient to overcome the rejection.

The rejections are restated below as the apply to new claims 1-10 and 15.

Claims 1-10 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant human ribonuclease inhibitor comprising the amino acid sequence of SEQ ID NO: 3, wherein said mutation is a

substitution in at least one of its two adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease, does not reasonably provide enablement for any mutant ribonuclease inhibitor having at least one amino acid substitution in at least one of its adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-10 and 15 are so broad as to encompass any mutant ribonuclease inhibitor having at least one amino acid substitution in at least one of its adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant ribonuclease inhibitors broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's

sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the mutant human ribonuclease inhibitor wherein said mutation is a substitution in at least one of its two adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant ribonuclease which comprises said cysteine mutations because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting ribonuclease inhibitor activity and oxidative resistance; (B) the general tolerance of ribonuclease to modification and extent of such tolerance; (C) a rational and predictable scheme for

modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any ribonuclease inhibitor. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***Response to applicants arguments (submitted on 7/5/2001):***

Applicant argues the above rejections based on 112 first paragraph together.

Applicant argues that as the basis of the rejection suggests that the claims are too broad in that they extend beyond human ribonuclease inhibitor and beyond the specified amino acid substitutions, however, applicants state this is unclear, because claim 10 is included in the rejection and applicants submit that claim 10 encompasses only human ribonuclease inhibitor and the specifically recited residues. Applicants submission that claim 10 only encompasses human RI with the specific amino acid substitutions is not persuasive, because claim 10 is drawn to a "mutant human

ribonuclease inhibitor " wherein the substituted residue is in "t least" one of positions 95, 96, 329 and 330. Applicants comments are acknowledged, however, as the claim is to a "mutant human ribonuclease" having at least the specified substitutions, there is no such limitation on the actual claimed ribonuclease inhibitor, that it remains a human ribonuclease. A "mutant" is no longer "human" and having at least encompasses those plus additional substitutions.

Applicants further submit that applicants have provided a thesis as to why ribonuclease inhibition has its well-known susceptibility to oxidation and that the adjacent cysteine residues are the most likely to be oxidized causing this characteristic inhibition.

Further applicants submit that in addition to the above theoretical explanation as to why modifications of the claimed category are effective, applicants submit other non-human ribonuclease inhibitors with a best fit analysis, thus making a full written description of several variants of the application in the specification.

Applicants further submit that for the above reasons the claims are fully enabled to the breadth of the subject matter claimed.

Applicants further submit that contrary to the above rejection, applicants have demonstrated regions of the protein structure which can be modified without effecting ribonuclease activity.

Applicants complete argument as it applies to claims 1-10 and 15 in response to both of the above rejections under 112 first paragraph is acknowledged, however, found non-persuasive.

With respect to written description, applicants are reminded that while applicants specification provides two examples of ribonuclease inhibitors that could possibly be mutated as required by the claims, two species is not sufficient to adequately describe the genus of claims which includes any and all such ribonuclease inhibitors. The specification also fails to describe additional representative species of these mutant ribonuclease inhibitors by sufficient **structural characteristics** or properties other than the activities recited in claim 1 and the disclosed cysteine modifications, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

With respect to the enablement of the claimed genus, applicants specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant ribonuclease which **does not** comprise said cysteine mutations because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting ribonuclease inhibitor activity and oxidative resistance; (B) the general tolerance of ribonuclease to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D)

the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any ribonuclease inhibitor. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Blazquez et al. (Journal of Biological Chemistry, Vol 271, pp 18638-18642, 1996).

Blazquez et al. teach a ribonuclease inhibitor which meets all of the structural limitations of the rejected claims and thus anticipates claims 1-10 and 15. The

ribonuclease inhibitor taught by Blazquez et al. is a mutant human ribonuclease having at least one amino acid substitution in at least one of two adjacent cysteine residues present in the amino acid sequence of the wild-type human ribonuclease inhibitor, the substitution being to an amino acid not capable of forming a disulfide bond with an adjacent residue. A greater resistance to oxidation (then the human ribonuclease inhibitor) and the specificity and binding affinity to ribonuclease are inherent properties of the ribonuclease inhibitor taught by Blazquez et al.

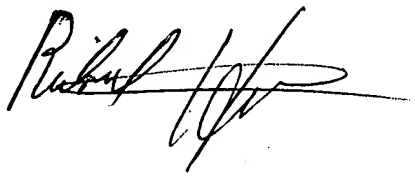
While the reference does not specifically disclose that the ribonuclease inhibitor has a greater resistance to oxidation (then the human ribonuclease inhibitor). Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax

phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
6/22/2005